AMENDMENTS TO THE DRAWINGS

The attached sheets of replacement formal drawings include changes to the Figures 2 to 6 as originally filed. Replacement Sheet 2/36, which includes Fig. 2A, replaces the originally filed Sheet 2/35 (previously designated as Figure 2). Replacement Sheet 3/36, which includes Fig. 2B, replaces the originally filed Sheet 3/35 (previously designated as Figure 2). Replacement Sheet 4/36, which includes Fig. 2C, replaces the originally filed Sheet 4/35 (previously designated as Figure 2). Replacement Sheet 5/36, which includes Fig. 3A, replaces the originally filed Sheet 5/35 (previously designated as Figure 3). Replacement Sheet 6/36, which includes Fig. 3B, replaces the originally filed Sheet 6/35 (previously designated as Figure 3). Replacement Sheet 7/36, which includes Fig. 3C, replaces the originally filed Sheet 7/35 (previously designated as Figure 3). Replacement Sheet 8/36, which includes Fig. 3D, replaces the originally filed Sheet 8/35 (previously designated as Figure 3). Replacement Sheet 9/36, which includes Fig. 4A, replaces the originally filed Sheet 9/35 (previously designated as Figure 4). Replacement Sheet 10/36, which includes Fig. 4B, replaces the originally filed Sheet 10/35 (previously designated as Figure 4). New Sheet 11/36 includes Fig. 4C (previously designated as Figure 4). Replacement Sheet 12/36, which includes Fig. 5A, replaces the originally filed Sheet 11/35 (previously designated as Figure 5). Replacement Sheet 12/36, which includes Figs. 5A and 5B, replaces the originally filed Sheet 11/35 (previously designated as Figure 5). Replacement Sheet 13/36, which includes Figs. 5C and 5D, replaces the originally filed Sheet 12/35 (previously designated as Figure 5). Replacement Sheet 14/36, which includes Figs. 5E and 5F, replaces the originally filed Sheet 13/35 (previously designated as Figure 5). Replacement Sheet 15/36, which includes Figs. 5G and 5H, replaces the originally filed Sheet 14/35 (previously designated as Figure 5).

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Replacement Sheet 16/36, which includes Figs. 5I and 5J, replaces the originally filed Sheet 15/35 (previously designated as Figure 5). Replacement Sheet 17/36, which includes Figs. 5K and 5L, replaces the originally filed Sheet 16/35 (previously designated as Figure 5). Replacement Sheet 18/36, which includes Figs. 5M and 5N, replaces the originally filed Sheet 17/35 (previously designated as Figure 5). Replacement Sheet 19/36, which includes Figs. 6A – 6C, replaces the originally filed Sheet 18/35 (previously designated as Figure 6). Replacement Sheet 20/36, which includes Figs. 6D – 6F, replaces the originally filed Sheet 19/35 (previously designated as Figure 6).

Attachments: Eighteen (18) replacement sheets formal drawings
One (1) new sheet of formal drawings
Eighteen (18) annotated sheets showing changes in red ink

REMARKS

Claims 1-35 are pending. Claims 1-35 stand rejected. No claims have been amended and the attached claim listing is provided for the convenience of the Examiner. Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. Reconsideration of the claims in light of the following remarks is requested.

Specification/Drawings

The Examiner objected to the specification because it does not comply with 37 C.F.R. § 1.84(u)(1), which requires that partial views of a drawing which are intended to form a complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. Specifically, Figures 2-6 are presented on several separate sheets, but are not labeled "Figure 2A, Figure 2B, etc." Additionally, the Brief Description of the Drawings does not contain "Figure 2A, Figure 2B, etc." Therefore, the specification has been amended to correct this informality. Replacement sheets for Figures 2A-2C, 3A-3D, 4A-4B, 5A-5G, and 6A-6B, and New sheet for Figure 4C are also submitted with this response. Annotated sheets showing changes marked in red ink are provided for the Examiner's convenience. No new matter is introduced with these amendments. Applicants respectfully request withdrawal of this objection.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1-35 are rejected under 35 U.S.C. §103(a) as allegedly obvious over the Bohn *et al.* patent (6,528,271 B1) ("Bohn") in view of Gurevich *et al.* (J. Biol. Chem. 270(2):720-731, 12 Jan 1995) ("Gurevich") and Hodgson (BIO/TECHNOLOGY 10; 973-877, 10 Sep. 1992 Publications) ("Hodgson"). Applicants respectfully traverse for the reasons that follow.

Applicants would like to provide the following brief summary to help distinguish the claimed invention from the cited art. The present claims are directed to methods of screening a composition for non-receptor-specific GPCR desensitization inhibitory activity. As noted in the Background section of the specification, a common limitation of GPCR-targeted drugs is a patient's ability to gain tolerance or resistance to such drugs, which is attributed to GPCRs desensitization in response to constant drug exposure (see paragraph [0007]). One possible approach to overcoming GPCR-based drug tolerance is to inhibit GPCR desensitization with compositions having GPCR desensitization inhibitory activity. Because several hundred human GPCRs are known, and because it is estimated that a couple thousand GPCRs exist in the human genome, it would be desirable to provide a method of screening compositions for inhibitory effect on GPCR desensitization that is not receptor specific (paragraph [0008]). As explained below, the prior art does not teach or suggest methods of screening a composition for non-receptor-specific GPCR desensitization inhibitory activity.

When rejecting claims under 35 U.S.C.§103(a), the Patent Office bears the burden of establishing a *prima facie* conclusion of obviousness. In order to do so, the Patent Office must demonstrate three elements: (1) that the prior art provides a suggestion or

motivation to modify or combine the teachings of the references relied upon by the Office to reject the claims; (2) that the prior art provides one of skill in the art with a reasonable expectation that the suggested combination or modification would be successful; and (3) that the prior art, either alone or in combination, teaches each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). These three elements are distinct. If any one is not established, *prima facie* obviousness is not established, and the Applicant is not required to show indicia of unobviousness, such as new or unanticipated results. *In re* Grabiak, 226 USPQ 870 (Fed. Cir. 1985).

The Patent Office alleges that Bohn teaches a method of identifying compounds that potentate receptor agonist activity by inhibiting the binding of β-arrestin to phosphorylated receptor. The Patent Office states that Gurevich teaches that it was well know in the art that the response of GPCRs like that of Bohn to continuous agonist activation diminished with time as a consequence of receptor desensitization. The Office alleges that the method of Bohn is only distinguished from the claimed method in that it lacks a comparative step employing a different receptor. The Office then relies on Hodgson's statements, to allegedly cure the deficiency of Bohn, "[f]irst you need all the receptors that are the plus targets - so that you are providing all the sites to which active compounds might bind. And then you need all the minus targets - so that you have can design away any negative effects. Applicants respectfully traverse.

As described, above Office alleges that the method of Bohn is only distinguished from the claimed method in that it lacks a comparative step employing a different

receptor. Applicants respectfully assert that the claimed methods do not include a comparative step as asserted by the Examiner. In contrasts, the pending claims include a combinative step with respect to different receptors. The methods of the present invention involve screening a test composition for an indication of GPCR desensitization inhibitory activity against two or more GPCRs that are different from each other. When there is an indication that a particular test composition has GPCR desensitization inhibitory activity with respect to each of the two or more GPCRs that are different from one another, then, according to the present invention, there is an indication that the test composition has non-receptor-specific GPCR desensitization inhibitory activity. Therefore, as described below, the claimed method requires indication from both the first receptor and an indication from the second receptor.

For example, Claim 1 provides in part:

(a) providing a first cell comprising a first GPCR [...]

(c) determining, [.....] whether or not the composition gives an indication of GPCR desensitization inhibitory activity with respect to the first GPCR;

(d) providing a second cell comprising a second GPCR different from the first GPCR [...]

(f) determining, [....] whether or not the composition gives an indication of GPCR desensitization inhibitory activity with respect to the second GPCR;

wherein an indication of GPCR desensitization inhibitory activity for the test composition in both step (c) and step (f) being an indication that the test composition has non-receptor-specific GPCR desensitization inhibitory activity (emphasis added).

Independent Claims 1, 13, 19 and 26 are directed to screening a composition for non-receptor-specific G-protein coupled receptor (GPCR) desensitization inhibitory activity. Applicants respectfully assert that none of the cited reverences teach or suggest a method of screening a composition for non-receptor-specific GPCR desensitization inhibitory activity as in Claims 1-35.

Bohn, Gurevich, *or* Hodgson, alone or in combination, do not teach or suggest the determining step (c) with respect to a first GPCR and determining step (f) with respect to second GPCR, wherein an indication of GPCR desensitization inhibitory activity for the test composition in both step (c) and step (f) being an indication that the test composition has non-receptor-specific GPCR desensitization inhibitory activity as required by independent Claims 1 and 13.

Likewise Bohn, Gurevich, *or* Hodgson, alone or in combination, do not teach or suggest the step (e) determining whether or not the composition has GPCR desensitization inhibitory activity with respect to the second GPCR; wherein an indication that the test composition has GPCR desensitization inhibitory activity with respect to <u>both</u> the first GPCR and the second GPCR being an indication that the test composition has non-receptor-specific GPCR desensitization inhibitory activity as required by independent Claim 19.

Bohn, Gurevich, *or* Hodgson, alone or in combination, do not teach or suggest step (c) determining whether or not the composition has GPCR desensitization inhibitory activity with respect to the first GPCR and with respect to the second GPCR, wherein an indication that the test composition has GPCR desensitization inhibitory activity with respect to both the first GPCR and the second GPCR being an indication that the test

composition has non-receptor-specific GPCR desensitization inhibitory activity as required by independent Claim 26.

In addition, none of the cited references provides a suggestion or the motivation to combine or modify their teachings to reach the present invention. The Patent Office states that "because it was known that GPCRs have important roles mediating fundamental physiological process such as vision, olfaction, cardiovascular function, and pain perception" as disclosed in column 1 of the Bohn *et al.* patent, one of ordinary skill would have been motivated not only to identify compounds that inhibit desensitization or a target receptor for the purpose of enhancing agonists activity on that receptor, that artisan would have been further motivated to include other GPCRs in such an assay to identify those compounds that **only** inhibit the desensitization of a target receptor or a set of receptors, such as opiod receptor of Bohn *et al.* for use in controlling pain, without inhibiting agonists desensitization of those GPCRs involved in mediation other fundamental physiological processes such as vision, olfaction, cardiovascular function *etc.* (emphasis in original). Again the Patent Office relies on Hodgson, stated that it would have been *prima facie* obvious to have include "all the minus targets" in the assay of Bohn for the purpose of identifying compounds that specifically inhibit the agonists desensitization of a target GPCR without affecting the agonists desensitization of other physiological receptors. Applicants respectfully disagree.

As the Patent Office is aware, a "prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983) (M.P.E.P. §2141.02 VI.) Hodgson teaches away from the present

invention, in particular relating to the screening of compositions for non-receptor-specific GPCR desensitization inhibitory activity. Applicants respectfully submit that the Hodgson reference is directed to the screening of compositions for receptor specific activity. Hodgson states [w]hen we do find selective agents and they appear to have selective activity, we will want to know whether that selectively make them more effective drugs (Hodgson at page 978). To screen for selective agents Hodgson teaches receptor specific screening *i.e.* using receptors that are the plus targets and receptors that are the minus targets to design away from non-receptor-specific screening.

Therefore, Hodgson teaches receptor specific screening instead of non-receptor-specific screening. Therefore, as a whole Hodgson teaches away from the present invention. Hodgson cannot be properly combined with Bohn and/or Gurevich to form an obviousness rejection. Due the above reasons, Applicants believe that the Patent Office has not established a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully requests that the rejection of independent Claim 1, 13, 19 and 29 under 35 U.S.C. § 103 (a) over Bohn, Gurevich, and Hodgson be withdrawn. All of the remaining claims ultimately depend from independent Claims 1, 13, 19 and 26, and are patentable for at least the same reasons. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: May 23, 2006 By: Michael Kolman

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FIG. 2A

~~FIG. 2~~

Human G Protein Coupled Receptor Family
(Receptors known as of January, 1999)

CLASS LIGAND	NUMBER	TISSUE	PHYSIOLOGY	THERAPEUTICS
•**Class I**				
Rhodopsin like				
•Amine				
•Acetylcholine (muscarinic & nicotinic)	5	Brain, Nerves, Heart	Neurotransmitter	Acuity, Alzheimer's
•Adrenoceptors				
•Alpha Adrenoceptors	6	Brain, Kidney, Lung	Gluconeogenesis	Diabetes, Cardiovascular
•Beta Adrenoceptors	3	Kidney, Heart	Muscle Contraction	Cardiovascular, Respiratory
•Dopamine	5	Brain, Kidney, GI	Neurotransmitter	Cardiovascular, Parkinson's
•Histamine	2	Vascular, Heart, Brain	Vascular Permeability	Anti-inflammatory, Ulcers
•Serotonin (5-HT)	16	Most Tissues	Neurotransmitter	Depression, Insomnia, Analgesic
•Peptide				
•Angiotensin	2	Vascular, Liver, Kidney	Vasoconstriction	Cardiovascular, Endocrine
•Bradykinin	1	Liver, Blood	Vasodilation,	Anti-inflammatory, Asthma
•C5a anaphylatoxin	1	Blood	Immune System	Anti-inflammatory
•Fmet-leu-phe	3	Blood	Chemoattractant	Anti-inflammatory
•Interleukin-8	1	Blood	Chemoattractant	Anti-inflammatory
•Chemokine	6	Blood	Chemoattractant	Anti-inflammatory
•Orexin	2	Brain	Fat Metabolism	Obesity
•Nociceptin	1	Brain	Bronchodilator, Pain	Airway Diseases, Anesthetic
•CCK (Gastrin)	2	Gastrointestinal	Motility, Fat Absorption	Gastrointestinal, Obesity, Parkinson's
•Endothelin	2	Heart, Bronchus, Brain	Muscle Contraction	Cardiovascular, Respiratory
•Melanocortin	5	Kidney, Brain	Metabolic Regulation	Anti-inflammatory, Analgesics
•Neuropeptide Y	5	Nerves, Intestine, Blood	Neurotransmitter	Behavior, Memory, Cardiovascular
•Neurotensin	1	Brain,	CNS	Cardiovascular, Analgesic
•Opioid	3	Brain,	CNS	Depression, Analgesic
•Somatostatin	5	Brain, Gastrointestinal	Neurotransmitter	Oncology, Alzheimer's

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FIG 2B

~~FIG. 2 (cont.)~~

•Tachykinin (Substance P, NKA_1)	3	Brain Nerves	Neurohormone	Depression, Analgesic
•Thrombin	3	Platelets, Blood Vessels	Coagulation	Anti-coagulant, Anti-inflammatory
•Vasopressin-like	4	Arteries, Heart, Bladder	Water Balance	Anti-diuretic, Diabetic Complications
•Galanin	1	Brain, Pancreas	Neurotransmitter	Analgesics, Alzheimer's
•Hormone protein				
•Follicle stimulating hormone	1	Ovary, Testis	Endocrine	Infertility
•Lutropin-choriogonadotropic	1	Ovary, Testis	Endocrine	Infertility
•Thyrotropin	1	Thyroid	Endocrine	Thyroidism, Metabolism
• (Rhod)opsin				
•Opsin	5	Eye	Photoreception	Ophthalmic Diseases
•Olfactory	4(~1000)	Nose	Smell	Olfactory Diseases
•Prostanoid				
•Prostaglandin	5	Arterial, Gastrointestinal	Vasodilation, Pain	Cardiovascular, Analgesic
•Lysophosphatidic Acid	2	Vessels, Heart, Lung	Inflammation	Cancer, Anti-Inflammatory
•Sphingosine-1-phosphate	2	Most Cells	Cell proliferation	Cancer
•Leukotriene	1	White Blood Cells, Bronchus	Inflammation	Asthma, Rheumatoid Arthritis
•Prostacyclin	1	Arterial, Gastrointestinal	Platelet Regulation	Cardiovascular
•Thromboxane	1	Arterial, Bronchus	Vasoconstriction	Cardiovascular, Respiratory
•Nucleotide-like				
•Adenosine	4	Vascular, Bronchus	Multiple Effects	Cardiovascular, Respiratory
•Purinoceptors	4	Vascular, Platelets	Relaxes Muscle	Cardiovascular, Respiratory
•Cannabis	2	Brain	Sensory Perception	Analgesics, Memory
•Platelet activating factor	1	Most Peripheral Tissues	Inflammation	Anti-inflammatory, Anti-asthmatic
•Gonadotropin-releasing hormone like				
•Gonadotropin-releasing hormone	1	Reproductive Organs, Pituitary	Reproduction	Prostate Cancer, Endometriosis
•Thyrotropin-releasing hormone	1	Pituitary, Brain	Thyroid Regulation	Metabolic Regulation
•Growth hormone-inhibiting factor	1	Gastrointestinal	Neuroendocrine	Oncology, Alzheimer's
•Melatonin	1	Brain, Eye, Pituitary	Neuroendocrine	Regulation of Circadian Cycle

ANNOTATED SHEET

FIG. 2c

~~FIG. 2 (cont.)~~

•Class II				
Secretin like				
•Secretin	1	Gastrointestinal, Heart	Digestion	Obesity, Gastrointestinal
•Calcitonin	1	Bone, Brain	Calcium Resorption	Osteoporosis
•Corticotropin releasing factor/urocortin	1	Adrenal, Vascular, Brain	Neuroendocrine	Stress, Mood, Obesity
•Gastric inhibitory peptide (GIP)	1	Adrenals, Fat Cells	Sugar/Fat Metabolism	Diabetes, Obesity
•Glucagon	1	Liver, Fat Cells, Heart	Gluconeogenesis	Cardiovascular
•Glucagon-like Peptide 1 (GLP-1)	1	Pancreas, Stomach, Lung	Gluconeogenesis	Cardiovascular, Diabetes, Obesity
•Growth hormone-releasing hormone	1	Brain	Neuroendocrine	Growth Regulation
•Parathyroid hormone	1	Bone, Kidney	Calcium Regulation	Osteoporosis
•PACAP	1	Brain, Pancreas, Adrenals	Metabolism	Metabolic Regulation
•Vasoactive intestinal polypeptide (VIP)	1	Gastrointestinal	Motility	Gastrointestinal
•Class III				
•Metabotropic Glutamate	7	Brain	Sensory Perception	Hearing, Vision
•$GABA_B$	1	Brain	Neurotransmitter	Mood Disorders
•Extracellular Calcium Sensing	1	Parathyroid, Kidney, GI Tract	Calcium Regulation	Cataracts, GI Tumors

ANNOTATED SHEET

FIGURE 3A
~~Figure 3~~

G protein-coupled receptors:
(Division into Class A
Or Class B)

1. **A1 adenosine receptor** [Homo sapiens]. ACCESSION AAB25533
NPIVYAF RIQKFRVTFL KIWNDHFRCQ PAPPIDEDLP EERPDD
Class A

2. **adrenergic, alpha -1B-, receptor** [Homo sapiens]. ACCESSION NP_000670
npiiypc sskefkrafv rilgcqcrgr grrrrrrrr lggcaytyrp wtrggslers qsrkdsldds gsclsgsqrt lpsaspspgy lgrgapppve lcafpewkap gallslpape ppgrrgrhds gplftfkllt epespgtdgg asnggceaaa dvangqpgfk snmplapgqf
Class A

3. **adrenergic receptor alpha-2A** [Homo sapiens]. ACCESSION AAG00447
npviytifn hdfrrafkki lcrgdrkriv
Class A

4. **alpha-2B-adrenergic receptor** - human. ACCESSION A37223
npviytifn qdfrrafrri lcrpwtqtaw
Class A

5. **alpha-2C-adrenergic receptor** - human. ACCESSION A31237
npviytvfn qdfrpsfkhi lfrrrrrgfr q
Class A

6. **beta-1-adrenergic receptor** [Homo sapiens]. ACCESSION NP_000675
npiiycrs pdfrkafqgl lccarraarr rhathgdrpr asgclarpgp ppspgaasdd ddddvvgatp parllepwag cnggaaadsd ssldepcrpg faseskv
Class A

7. **beta-2 adrenergic receptor**. ACCESSION P07550
npliycrsp dfriafqell clrrsslkay gngyssngnt 361 geqsgyhveq ekenkllced lpgtedfvgh qgtvpsdnid sqgrncstnd sll
Class A

8. **dopamine receptor D1** [Homo sapiens]. ACCESSION NP_000785
npii yafnadfrka fstllgcyrl cpatnnaiet vsinnngaam fsshheprgs iskecnlvyl iphavgssed lkkeeaagia rpleklspal svildydtdv slekiqpitq ngqhpt
Class A

9. **D(2) dopamine receptor.** ACCESSION P14416
npiiyttfn iefrkaflki lhc
Class A

FIG. 3B

~~Figure 3 (cont.)~~

10. **d3 dopamine receptor** - human. ACCESSION G01977
np viyttfnief rkaflkilsc
Class A

11. **dopamine receptor D4** - human. ACCESSION DYHUD4
npviytv fnaefrnvfr kalracc
Class A

12. **dopamine receptor D5** - human. ACCESSION DYHUD5
npviya fnadfqkvfa qllgcshfcs rtpvetvnis nelisynqdi vfhkeiaaay ihrmmpnavtp gnrevdndee egpfdrmfqi yqtspdgdpv aesvweldce geisldkitp ftpngfh
Class A

13. **muscarinic acetylcholine receptor M1** [Homo sapiens]. ACCESSION NP_000729
npmcyal cnkafrdtfr llllcrwdkr rwrkipkrpg svhrtpsrqc
Class A

14. **muscarinic acetylcholine receptor M2** [Homo sapiens]. ACCESSION NP_000730
npacy alcnatfkkt fkhllmchyk nigatr
Class A

15. **muscarinic acetylcholine receptor M3 [Homo sapiens].** ACCESSION NP_000731
n pvcyalcnkt frttfkmlll cqcdkkkrrk qqyqqrqsvi fhkrapeqal
Class A

16. **muscarinic acetylcholine receptor M4** [Homo sapiens]. ACCESSION NP_000732
npa cyalcnatfk ktfrhlllcq yrnigtar
Class A

17. **m5 muscarinic receptor.** locus HUMACHRM ACCESSION AAA51569
npicyalcnr tfrktfkmll lcrwkkkkve eklywqgnsk lp
Class A

18. **5-hydroxytryptamine (serotonin) receptor 1A** [Homo sapiens]. ACCESSION BAA90449
npviy ayfnkdfqna fkkiikckf
Class A

19. **5-hydroxytryptamine (serotonin) receptor 1B** [Homo sapiens]. ACCESSION BAA94455
npiiyt msnedfkqaf hklirfkcts
Class A

20. **5-hydroxytryptamine (serotonin) receptor 1E** [Homo sapiens]. ACCESSION BAA94458
n pllytsfned fklafkklir cre
Class A

FIG. 3C

~~Figure 3 (cont.)~~

21. **OLFACTORY RECEPTOR 6A1**. ACCESSION O95222
npiiyclmq evkralccil hlyqhqdpdp kkgsmv
Class A

22. **OLFACTORY RECEPTOR 2C1**. ACCESSION O95371
npliy tlmmevkga lrrllgkgre vg
Class A

23. **angiotensin receptor 1 [Homo sapiens]**. ACCESSION NP_033611
npl fygflgkkfk ryflqllkyi ppkakshsnl sfkmsflsyr psdnvssstk kpapcfeve
Class B

24. **angiotensin receptor 2** [Homo sapiens]. ACCESSION NP_000677
npflycf vgnrfqqklr svfrvpitwl qgkresmscr kssslremet fvs
Class B

25. **interleukin 8 receptor beta (CXCR2)** [Homo sapiens]. ACCESSION NM_001557
NPLIYAFIGQKFRHGLLKILAIHGLISKDSLPKDSRPSFVGSSSGHTSTTL
Class B

26. **cx3c chemokine receptor 1** (cx3cr1) (fractalkine receptor)
ACCESSION P49238
np liyafagekf rrylyhlygk clavlcgrsv hvdfsssesq rsrhgsvlss nftyhtsdgd allll
Class B

27. **neurotensin receptor - human.** ACCESSION S29506
n pilynlvsan frhiflatla clcpvwrrrr krpafsrkad svssnhflss natretly
Class B

28. **SUBSTANCE-P RECEPTOR (SPR)** (NK-1 RECEPTOR) (NK-1R). ACCESSION P25103
npiiyccInd rfrlgfkhaf rccpfisagd yeglemkstr ylqtqgsvyk vsrlettistvvgaheeepe dgpkatpssl
dltsncssrs dsktmtesfs fssnvls
Class B

29. **vasopressin receptor type 2** [Homo sapiens]. ACCESSION AAD16444
npwiyasfss svsselrsll ccargrtpps lgpqdesctt assslakdts s
Class B

30. **thyrotropin-releasing hormone receptor** - human. ACCESSION JN0708
npviy nlmsqkfraa frklcnckqk ptekpanysv alnysvikes dhfstelddi tvtdtylsat kvsfddtcla sevsfsqs
Class B

FIG 3D

~~Figure 3 (cont.)~~

31. **oxytocin receptor - human.** ACCESSION A55493
npwiym lftghlfhel vqrflccsas ylkgrrlget saskksnsss fvlshrsssq rscsqpsta
Class B

32. **neuromedin U receptor [Homo sapiens].** ACCESSION AAG24793
npvlyslmssrfretfqealclgacchrlrprhsshslsrmttgstlcdvgslgswvhplagndgpeaqqetdps
Class B

33. **gastrin receptor.** ACCESSION AAC37528
nplvy cfmhrrfrqa cletcarccp rpprarpral pdedpptpsi aslsrlsytt istlgpg
Class B

34. **galanin receptor 3 [Homo sapiens].** ACCESSION 10879541
nplv yalasrhfra rfrrlwpcgr rrrhrarral rrvrpassgp pgcpgdarps grllagggqg pepregpvhg geaargpe
Class A

35. **edg-1** - human. ACCESSION A35300
npiiy tltnkemrra firimscckc psgdsagkfk rpiiagmefs rsksdnsshp 361 qkdegdnpet imssgnvnss s
Class A

36. **central cannabinoid receptor** [Homo sapiens]. ACCESSION NP_057167
npiiyalr skdlrhafrs mfpscegtaq pldnsmgdsd clhkhannaa svhraaesci kstvkiakvt msvstdtsae al
Class A

37. **delta opioid receptor** - human. ACCESSION I38532
npvlyaf ldenfkrcfr qlcrkpcgrp dpssfsrpre atarervtac tpsdgpgggr aa
Class A

38. proteinase activated receptor 2 (PAR-2) human. ACCESSION P55085
dpfvyyfvshdfrdhaknallcrsvrtvkqmqvsltskkhsrksssysssstvktsy
Class A

39. **vasopressive intestinal peptide receptor (VIPR) rat**. ACCESSION NM_012685
NGEVQAELRRKWRRWHLQGVLGWSSKSQHPWGGSNGATCSTQVSMLTRVSPSARR
SSSFQAEVSLV
Class B

FIG. 4A

FIGURE 4

The mutated amino acid at the second position of the DRY motif is underlined.

VASOPRESSIN V2 RECEPTOR - (Human)
accession P30518

R137H

```
  1 MLMASTTSAV PGHPSLPSLP SNSSQERPLD TRDPLLARAE LALLSIVFVA VALSNGLVLA
 61 ALARRGRRGH WAPIHVFIGH LCLADLAVAL FQVLPQLAWK ATDRFRGPDA LCRAVKYLQM
121 VGMYASSYMI LAMTLDHHRA ICRPMLAYRH GSGAHWNRPV LVAWAFSLLL SLPQLFIFAQ
181 RNVEGGSGVT DCWACFAEPW GRRTYVTWIA LMVFVAPTLG IAACQVLIFR EIHASLVPGP
241 SERPGGRRRG RRTGSPGEGA HVSAAVAKTV RMTLVIVVVY VLCWAPFFLV QLWAAWDPEA
301 PLEGAPFVLL MLLASLNSCT NPWIYASFSS SVSSELRSLL CCARGRTPPS LGPQDESCTT
361 ASSSLAKDTS S
```

(SEQ ID NO:40)

ALPHA-1B ADRENERGIC RECEPTOR (ALPHA 1B-ADRENOCEPTOR).
(Golden hamster)
ACCESSION P18841
R143E

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDEYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:41)

R143A

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDAYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:42)

FIG. 4B

~~FIG. 4 (cont.)~~

R143H

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDHYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:43)

R143N

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDNYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:44)

Angiotensin II Receptor, Type 1 (AT1A) [Rattus norvegicus].
ACCESSION NP_112247

[move to FIG.4C page]

R126H

```
  1 MALNSSAEDG IKRIQDDCPK AGRHSYIFVM IPTLYSIIFV VGIFGNSLVV IVIYFYMKLK
 61 TVASVFLLNL ALADLCFLLT CPLWAVYTAM EYRWPFGNHL CKIASASVTF NLYASVFLLT
121 CLSIDHYLAI VHPMKSRLRR TMLVAKVTCI IIWLMAGLAS LPAVIHRNVY FIENTNITVC
181 AFHYESRNST LPIGLGLTKN ILGFLFPFLI ILTSYTLIWK ALKKAYEIQK NKPRNDDIFR
241 IIMAIVLFFF FSWVPHQIFT FLDVLIQLGV IHDCKISDIV DTAMPITICI AYFNNCLNPL
301 FYGFLGKKFK KYFLQLLKYI PPKAKSHSSL STKMSTLSYR PSDNMSSSAK KPASCFEVE
```

(SEQ ID NO:45)

FIG. 4C

FIG. 4 (cont.)

R143H

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDHYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:43)

[move to FIG 4B page]

R143N

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDNYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:44)

Angiotensin II Receptor, Type 1 (AT1A) [Rattus norvegicus].
ACCESSION NP_112247

R126H

```
  1 MALNSSAEDG IKRIQDDCPK AGRHSYIFVM IPTLYSIIFV VGIFGNSLVV IVIYFYMKLK
 61 TVASVFLLNL ALADLCFLLT CPLWAVYTAM EYRWPFGNHL CKIASASVTF NLYASVFLLT
121 CLSIDHYLAI VHPMKSRLRR TMLVAKVTCI IIWLMAGLAS LPAVIHRNVY FIENTNITVC
181 AFHYESRNST LPIGLGLTKN ILGFLFPFLI ILTSYTLIWK ALKKAYEIQK NKPRNDDIFR
241 IIMAIVLFFF FSWVPHQIFT FLDVLIQLGV IHDCKISDIV DTAMPITICI AYFNNCLNPL
301 FYGFLGKKFK KYFLQLLKYI PPKAKSHSSL STKMSTLSYR PSDNMSSSAK KPASCFEVE
```

(SEQ ID NO:45)

FIGS. 5A - 5B

~~Figure 5~~

A. Amino Acid sequence of the hGPR3- Enhanced Receptor

MMWGAGSPLAWLSAGSGNVNVSSVGPAEGPTGPAAPLPSPKAWDVVLCISGTLVSCENA
LVVAIIVGTPAFRAPMFLLVGSLAVADLLAGLGLVLHFAAVFCIGSAEMSLVLVGVLAM
AFTASIGSLLAITVDRYLSLYNALTYYSETTVTRTYVMLALVWGGALGLGLLPVLAWNC
LDGLTTCGVVYPLSKNHLVVLAIAFFMVFGIMLQLYAQICRIVCRHAQQIALQRHLLPA
SHYVATRKGIATLAVVLGAFAACWLPFTVYCLLGDAHSPPLYTYLTLLPATYNSMINPI
IYAFRNQDVQKVLWAVCCCCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(SEQ ID No: 46)

B. Nucleotide sequence of the hGPR3- Enhanced Receptor

ATGATGTGGGGTGCAGGCAGCCCTCTGGCCTGGCTCTCAGCTGGCTCAGGCAACGTGAA
TGTAAGCAGCGTGGGCCCAGCAGAGGGGCCCACAGGTCCAGCCGCACCACTGCCCTCGC
CTAAGGCCTGGGATGTGGTGCTCTGCATCTCAGGCACCCTGGTGTCCTGCGAGAATGCG
CTAGTGGTGGCCATCATCGTGGGCACTCCTGCCTTCCGTGCCCCCATGTTCCTGCTGGT
GGGCAGCCTGGCCGTGGCAGACCTGCTGGCAGGCCTGGGCCTGGTCCTGCACTTTGCTG
CTGTCTTCTGCATCGGCTCAGCGGAGATGAGCCTGGTGCTGGTTGGCGTGCTGGCAATG
GCCTTTACYGCCAGCATCGGCAGTCTACTGGCCATCACTGTCGACCGCTACCTTTCTCT
GTACAATGCCCTCACCTACTATTCAGAGACAACAGTGACACGGACCTATGTGATGCTGG
CCTTAGTGTGGGGAGGTGCCCTGGGCCTGGGGCTGCTGCCTGTGCTGGCCTGGAACTGC
CTGGATGGCCTGACCACATGTGGCGTGGTTTATCCACTCTCCAAGAACCATCTGGTAGT
TCTGGCCATTGCCTTCTTCATGGTGTTTGGCATCATGCTGCAGCTCTACGCCCAAATCT
GCCGCATCGTCTGCCGCCATGCCCAGCAGATTGCCCTTCAGCGGCACCTGCTGCCTGCC
TCCCACTATGTGGCCACCCGCAAGGGCATTGCCACACTGGCCGTGGTGCTTGGAGCCTT
TGCCGCCTGCTGGTTGCCCTTCACTGTCTACTGCCTGCTGGGTGATGCCCACTCTCCAC
CTCTCTACACCTATCTTACCTTGCTCCCTGCCACCTACAACTCCATGATCAACCCTATC
ATCTACGCCTTCCGCAACCAGGATGTGCAGAAAGTGCTGTGGGCTGTCTGCTGCTGCTG
TGCGGCCGCACGGGGACGCACCCCACCCAGCCTGGGTCCCCAAGATGAGTCCTGCACCA
CCGCCAGcTCCTCCCTGGCCAAGGACACTTCATCGTGA
(SEQ ID No: 47)

FIGS. 5C - 5D

Figure 5 ~~(continued)~~

C. Amino Acid sequence of the hGPR6- Enhanced Receptor

MNASAASLNDSQVVVVAAEGAAAAATAAGGPDTGEWGPPAAAALGAGGGANGSLELSSQ
LSAGPPGLLLPAVNPWDVLLCVSGTVIAGENALVVALIASTPALRTPMFVLVGSLATAD
LLAGCGLILHFVFQYLVPSETVSLLTVGFLVASFAASVSSLLAITVDRYLSLYNALTYY
SRRTLLGVHLLLAATWTVSLGLGLLPVLGWNCLAERAACSVVRPLARSHVALLSAAFFM
VFGIMLHLYVRICQVVWRHAHQIALQQHCLAPPHLAATRKGVGTLAVVLGTFGASWLPF
AIYCVVGSHEDPAVYTYATLLPATYNSMINPIIYAFRNQEIQRALWLLLCGCAAARGRT
PPSLGPQDESCTTASSSLAKDTSS
(SEQ ID No: 48)

D. Nucleotide sequence of the hGPR6- Enhanced Receptor

ATGAACGCGAGCGCCGCCTCGCTCAACGACTCCCAGGTGGTGGTAGTGGCGGCCGAAGG
AGCGGCGGCGGCGGCCACAGCAGCAGGGGGGCCGGACACGGGCGAATGGGGACCCCCTG
CTGCGGCGGCTCTAGGAGCCGGCGGCGGAGCTAATGGGTCTCTGGAGCTGTCCTCGCAG
CTGTCGGCTGGGCCACCGGGACTCCTGCTGCCAGCGGTGAATCCGTGGGACGTGCTCCT
GTGCGTGTCGGGGACAGTGATCGCTGGAGAAAACGCGCTGGTGGTGGCGCTCATCGCGT
CCACTCCGGCGCTGCGCACGCCCATGTTCGTGCTGGTAGGCAGCCTGGCCACCGCTGAC
CTGTTGGCGGGCTGTGGCCTCATCTTGCACTTTGTGTTCCAGTACTTGGTGCCCTCGGA
GACTGTGAGTCTGCTCACGGTGGGCTTCCTCGTGGCCTCCTTCGCCGCCTCTGTCAGCA
GCCTGCTGGCCATTACGGTGGACCGCTACCTGTCCCTGTATAACGCGCTCACCTATTAC
TCGCGCCGGACCCTGTTGGGCGTGCACCTCCTGCTTGCCGCCACTTGGACCGTGTCCCT
AGGCCTGGGGCTGCTGCCCGTGCTGGGCTGGAACTGCCTGGCAGAGCGCGCCGCCTGCA
GCGTGGTGCGCCCGCTGGCGCGCAGCCACGTGGCTCTGCTCTCCGCCGCCTTCTTCATG
GTCTTCGGCATCATGCTGCACCTGTACGTGCGCATCTGCCAGGTGGTCTGGCGCCACGC
GCACCAGATCGCGCTGCAGCAGCACTGCCTGGCGCCACCCCATCTCGCTGCCACCAGAA
AGGGTGTGGGTACACTGGCTGTGGTGCTGGGCACTTTCGGCGCCAGCTGGCTGCCCTTC
GCCATCTATTGCGTGGTGGGCAGCCATGAGGACCCGGCGGTCTACACTTACGCCACCCT
GCTGCCCGCCACCTACAACTCCATGATCAATCCCATCATCTATGCCTTCCGCAACCAGG
AGATCCAGCGCGCCCTGTGGCTCCTGCTCTGTGGCTGTGCGGCCGCACGGGGACGCACC
CCACCCAGCCTGGGTCCCCAAGATGAGTCCTGCACCACCGCCAGCTCCTCCCTGGCCAA
GGACACTTCATCGTGA
(SEQ ID No: 49)

FIGS. 5E-5F

~~Figure 5 (continued)~~

E. Amino Acid sequence of the hGPR12- Enhanced Receptor

MNEDLKVNLSGLPRDYLDAAAAENISAAVSSRVPAVEPEPELVVNPWDIVLCTSGTLIS
CENAIVVLIIFHNPSLRAPMFLLIGSLALADLLAGIGLITNFVFAYLLQSEATKLVTIG
LIVASFSASVCSLLAITVDRYLSLYYALTYHSERTVTFTYVMLVMLWGTSICLGLLPVM
GWNCLRDESTCSVVRPLTKNNAAILSVSFLFMFALMLQLYIQICKIVMRHAHQIALQHH
FLATSHYVTTRKGVSTLAIILGTFAACWMPFTLYSLIADYTYPSIYTYATLLPATYNSI
INPVIYAFRNQEIQKALCLICCGCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(SEQ ID No: 50)

F. Nucleotide sequence of the hGPR12- Enhanced Receptor

ATGAATGAAGACCTGAAGGTCAATTTAAGCGGGCTGCCTCGGGATTATTTAGATGCCGC
TGCTGCGGAGAACATCTCGGCTGCTGTCTCCTCCCGGGTTCCTGCCGTAGAGCCAGAGC
CTGAGCTCGTAGTCAACCCCTGGGACATTGTCTTGTGTACCTCGGGAACCCTCATCTCC
TGTGAAAATGCCATTGTGGTCCTTATCATCTTCCACAACCCCAGCCTGCGAGCACCCAT
GTTCCTGCTAATAGGCAGCCTGGCTCTTGCAGACCTGCTGGCCGGCATTGGACTCATCA
CCAATTTTGTTTTTGCCTACCTGCTTCAGTCAGAAGCCACCAAGCTGGTCACGATCGGC
CTCATTGTCGCCTCTTTCTCTGCCTCTGTCTGCAGCTTGCTGGCTATCACTGTTGACCG
CTACCTCTCACTGTACTACGCTCTGACGTACCATTCGGAGAGGACGGTCACGTTTACCT
ATGTCATGCTCGTCATGCTCTGGGGGACCTCCATCTGCCTGGGGCTGCTGCCCGTCATG
GGCTGGAACTGCCTCCGAGACGAGTCCACCTGCAGCGTGGTCAGACCGCTCACCAAGAA
CAACGCGGCCATCCTCTCGGTGTCCTTCCTCTTCATGTTTGCGCTCATGCTTCAGCTCT
ACATCCAGATCTGTAAGATTGTGATGAGGCACGCCCATCAGATAGCCCTGCAGCACCAC
TTCCTGGCCACGTCGCACTATGTGACCACCCGGAAAGGGGTCTCCACCCTGGCTATCAT
CCTGGGGACGTTTGCTGCTTGCTGGATGCCTTTCACCCTCTATTCCTTGATAGCGGATT
ACACCTACCCCTCCATCTATACCTACGCCACCCTCCTGCCCGCCACCTACAATTCCATC
ATCAACCCTGTCATATATGCTTTCAGAAACCAAGAGATCCAGAAAGCGCTCTGTCTCAT
TTGCTGCGGCTGCGCGGCCGCACGGGGACGCACCCCACCCAGCCTGGGTCCCCAAGATG
AGTCCTGCACCACCGCCAGCTCCTCCCTGGCCAAGGACACTTCATCGTGA
(SEQ ID No: 51)

FIGS. 5G-5H

~~Figure 5 (continued)~~

G. Amino Acid sequence of the hSREB3- Enhanced Receptor

MANTTGEPEEVSGALSPPSASAYVKLVLLGLIMCVSLAGNAILSLLVLKERALHKAPYY
FLLDLCLADGIRSAVCFPFVLASVRHGSSWTFSALSCKIVAFMAVLFCFHAAFMLFCIS
VTRYMAIAHHRFYAKRMTLWTCAAVICMAWTLSVAMAFPPVFDVGTYKFIREEDQCIFE
HRYFKANDTLGFMLMLAVLMAATHAVYGKLLLFEYRHRKMKPVQMVPAISQNWTFHGPG
ATGQAAANWIAGFGRGPMPPTLLGIRQNGHAASRRLLGMDEVKGEKQLGRMFYAITLLF
LLLWSPYIVACYWRVFVKACAVPHRYLATAVWMSFAQAAVNPIVCFLLNKDLKKCLRTH
APCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(SEQ ID No: 52)

H. Nucleotide sequence of the hSREB3- Enhanced Receptor

ATGGCCAACACTACCGGAGAGCCTGAGGAGGTGAGCGGCGCTCTGTCCCCACCGTCCGC
ATCAGCTTATGTGAAGCTGGTACTGCTGGGACTGATTATGTGCGTGAGCCTGGCGGGTA
ACGCCATCTTGTCCCTGCTGGTGCTCAAGGAGCGTGCCCTGCACAAGGCTCCTTACTAC
TTCCTGCTGGACCTGTGCCTGGCCGATGGCATACGCTCTGCCGTCTGCTTCCCCTTTGT
GCTGGCTTCTGTGCGCCACGGCTCTTCATGGACCTTCAGTGCACTCAGCTGCAAGATTG
TGGCCTTTATGGCCGTGCTCTTTTGCTTCCATGCGGCCTTCATGCTGTTCTGCATCAGC
GTCACCCGCTACATGGCCATCGCCCACCACCGCTTCTACGCCAAGCGCATGACACTCTG
GACATGCGCGGCTGTCATCTGCATGGCCTGGACCCTGTCTGTGGCCATGGCCTTCCCAC
CTGTCTTTGACGTGGGCACCTACAAGTTTATTCGGGAGGAGGACCAGTGCATCTTTGAG
CATCGCTACTTCAAGGCCAATGACACGCTGGGCTTCATGCTTATGTTGGCTGTGCTCAT
GGCAGCTACCCATGCTGTCTACGGCAAGCTGCTCCTCTTCGAGTATCGTCACCGCAAGA
TGAAGCCAGTGCAGATGGTGCCAGCCATCAGCCAGAACTGGACATTCCATGGTCCCGGG
GCCACCGGCCAGGCTGCTGCCAACTGGATCGCCGGCTTTGGCCGTGGGCCCATGCCACC
AACCCTGCTGGGTATCCGGCAGAATGGGCATGCAGCCAGCCGGCGGCTACTGGGCATGG
ACGAGGTCAAGGGTGAAAAGCAGCTGGGCCGCATGTTCTACGCGATCACACTGCTCTTT
CTGCTCCTCTGGTCACCCTACATCGTGGCCTGCTACTGGCGAGTGTTTGTGAAAGCCTG
TGCTGTGCCCCACCGCTACCTGGCCACTGCTGTTTGGATGAGCTTCGCCCAGGCTGCCG
TCAACCCAATTGTCTGCTTCCTGCTCAACAAGGACCTCAAGAAGTGCCTGAGGACTCAC
GCCCCCTGCGCGGCCGCACGGGGACGCACCCCACCCAGCCTGGGTCCCCAAGATGAGTC
CTGCACCACCGCCAGCTCCTCCCTGGCCAAGGACACTTCATCGTGA
(SEQ ID No: 53)

FIGS. 5I-5J

Figure 5 (continued)

I. Amino Acid sequence of the hSREB2- Enhanced Receptor

MANYSHAADNILQNLSPLTAFLKLTSLGFIIGVSVVGNLLISILLVKDKTLHRAPYYFL
LDLCCSDILRSAICFPFVFNSVKNGSTWTYGTLTCKVIAFLGVLSCFHTAFMLFCISVT
RYLAIAHHRFYTKRLTFWTCLAVICMVWTLSVAMAFPPVLDVGTYSFIREEDQCTFQHR
SFRANDSLGFMLLLALILLATQLVYLKLIFFVHDRRKMKPVQFVAAVSQNWTFHGPGAS
GQAAANWLAGFGRGPTPPTLLGIRQNANTTGRRRLLVLDEFKMEKRISRMFYIMTFLFL
TLWGPYLVACYWRVFARGPVVPGGFLTAAVWMSFAQAGINPFVCIFSNRELRRCFSTTL
LYCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(SEQ ID No: 54)

J. Nucleotide sequence of the hSREB2- Enhanced Receptor

ATGGCGAACTATAGCCATGCAGCTGACAACATTTTGCAAAATCTCTCGCCTCTAACAGC
CTTTCTGAAACTGACTTCCTTGGGTTTCATAATAGGAGTCAGCGTGGTGGGCAACCTCC
TGATCTCCATTTTGCTAGTGAAAGATAAGACCTTGCATAGAGCACCTTACTACTTCCTG
TTGGATCTTTGCTGTTCAGATATCCTCAGATCTGCAATTTGTTTCCCATTTGTGTTCAA
CTCTGTCAAAAATGGCTCTACCTGGACTTATGGGACTCTGACTTGCAAAGTGATTGCCT
TTCTGGGGGTTTTGTCCTGTTTCCACACTGCTTTCATGCTCTTCTGCATCAGTGTCACC
AGATACTTAGCTATCGCCCATCACCGCTTCTATACAAAGAGGCTGACCTTTTGGACGTG
TCTGGCTGTGATCTGTATGGTGTGGACTCTGTCTGTGGCCATGGCATTTCCCCCGGTTT
TAGACGTGGGCACTTACTCATTCATTAGGGAGGAAGATCAATGCACCTTCCAACACCGC
TCCTTCAGGGCTAATGATTCCTTAGGATTTATGCTGCTTCTtGCTCTCATCCTCCTAGC
CACACAGCTTGTCTACCTCAAGCTGATATTTTTCGTCCACGATCGAAGAAAAATGAAGC
CAGTCCAGTTTGTAGCAGCAGTCAGCCAGAACTGGACTTTTCATGGTCCTGGAGCCAGT
GGCCAGGCAGCTGCCAATTGGCTAGCAGGATTTGGAAGGGGTCCCACACCACCCACCTT
GCTGGGCATCAGGCAAAATGCAAACACCACAGGCAGAAGAAGGCTATTGGTCTTAGACG
AGTTCAAAATGGAGAAAAGAATCAGCAGAATGTTCTATATAATGACTTTTCTGTTTCTA
ACCTTGTGGGGCCCCTACCTGGTGGCCTGTTATTGGAGAGTTTTTGCAAGAGGGCCTGT
AGTACCAGGGGGATTTCTAACAGCTGCTGTCTGGATGAGTTTTGCCCAAGCAGGAATCA
ATCCTTTTGTCTGCATTTTCTCAAACAGGGAGCTGAGGCGCTGTTTCAGCACAACCCTT
CTTTACTGCGCGGCCGCACGGGGACGCACCCCACCCAGCCTGGGTCCCCAAGATGAGTC
CTGCACCACCGCCAGCTCCTCCCTGGCCAAGGACACTTCATCGTGA
(SEQ ID No: 55)

FIGS. 5K-5L

~~Figure 5 (continued)~~

K. Amino Acid sequence of the hGPR8- Enhanced Receptor

MQAAGHPEPLDSRGSFSLPTMGANVSQDNGTGHNATFSEPLPFLYVLLPAVYSGICAVG
LTGNTAVILVILRAPKMKTVTNVFILNLAVADGLFTLVLPVNIAEHLLQYWPFGELLCK
LVLAVDHYNIFSSIYFLAVMSVDRYLVVLATVRSRHMPWRTYRGAKVASLCVWLGVTVL
VLPFFSFAGVYSNELQVPSCGLSFPWPERVWFKASRVYTLVLGFVLPVCTICVLYTDLL
RRLRAVRLRSGAKALGKARRKVTVLVLVVLAVCLLCWTPFHLASVVALTTDLPQTPLVI
SMSYVITSLSYANSCLNPFLYAFLDDNFRKNFRSILRCAAARGRTPPSLGPQDESCTTA
SSSLAKDTSS
(SEQ ID No: 56)

L. Nucleotide sequence of the hGPR8- Enhanced Receptor

ATGCAGGCCGCTGGGCACCCAGAGCCCCTTGACAGCAGGGGCTCCTTCTCCCTCCCCAC
GATGGGTGCCAACGTCTCTCAGGACAATGGCACTGGCCACAATGCCACCTTCTCCGAGC
CACTGCCGTTCCTCTATGTGCTCCTGCCCGCCGTGTACTCCGGGATCTGTGCTGTGGGG
CTGACTGGCAACACGGCCGTCATCCTTGTAATCCTAAGGGCGCCCAAGATGAAGACGGT
GACCAACGTGTTCATCCTGAACCTGGCCGTCGCCGACGGGCTCTTCACGCTGGTACTGC
CCGTCAACATCGCGGAGCACCTGCTGCAGTACTGGCCCTTCGGGGAGCTGCTCTGCAAG
CTGGTGCTGGCCGTCGACCACTACAACATCTTCTCCAGCATCTACTTCCTAGCCGTGAT
GAGCGTGGACCGATACCTGGTGGTGCTGGCCACCGTGAGGTCCCGCCACATGCCCTGGC
GCACCTACCGGGGGGCGAAGGTCGCCAGCCTGTGTGTCTGGCTGGGCGTCACGGTCCTG
GTTCTGCCCTTCTTCTCTTTCGCTGGCGTCTACAGCAACGAGCTGCAGGTCCCAAGCTG
TGGGCTGAGCTTCCCGTGGCCCGAGCGGGTCTGGTTCAAGGCCAGCCGTGTCTACACTT
TGGTCCTGGGCTTCGTGCTGCCCGTGTGCACCATCTGTGTGCTCTACACAGACCTCCTG
CGCAGGCTGCGGGCCGTGCGGCTCCGCTCTGGAGCCAAGGCTCTAGGCAAGGCCAGGCG
GAAGGTGACCGTCCTGGTCCTCGTCGTGCTGGCCGTGTGCCTCCTCTGCTGGACGCCCT
TCCACCTGGCCTCTGTCGTGGCCCTGACCACGGACCTGCCCCAGACCCCACTGGTCATC
AGTATGTCCTACGTCATCACCAGCCTCAGCTACGCCAACTCGTGCCTGAACCCCTTCCT
CTACGCCTTTCTAGATGACAACTTCCGGAAGAACTTCCGCAGCATATTGCGGTGCGCGG
CCGCACGGGGACGCACCCCACCCAGCCTGGGTCCCCAAGATGAGTCCTGCACCACCGCC
AGCTCCTCCCTGGCCAAGGACACTTCATCGTGA
(SEQ ID No: 57)

FIGS 5M-5N

~~Figure 5 (continued)~~

M. Amino Acid sequence of the hGPR22-Enhanced Receptor

MCFSPILEINMQSESNITVRDDIDDINTNMYQPLSYPLSFQVSLTGFLMLEIVLGLGSN
LTVLVLYCMKSNLINSVSNIITMNLHVLDVIICVGCIPLTIVILLLSLESNTALICCFH
EACVSFASVSTAINVFAITLDRYDISVKPANRILTMGRAVMLMISIWIFSFFSFLIPFI
EVNFFSLQSGNTWENKTLLCVSTNEYYTELGMYYHLLVQIPIFFFTVVVMLITYTKILQ
ALNIRIGTRFSTGQKKKARKKKTISLTTQHEATDMSQSSGGRNVVFGVRTSVSVIIALR
RAVKRHRERRERQKRVFRMSLLIISTFLLCWTPISVLNTTILCLGPSDLLVKLRLCFLV
MAYGTTIFHPLLYAFTRQKFQKVLKSKMKKRVVCAAARGRTPPSLGPQDESCTTASSSL
AKDTSS
(SEQ ID No: 58)

N. Nucleotide sequence of the hGPR22-Enhanced Receptor

ATGTGTTTTTCTCCcaTTCTGGAAATCAACATGCAGTCTGAATCTAACATTACAGTGCG
AGATGACATTGATGACATCAACACCAATATGTACCAACCACTATCATATCCGTTAAGCT
TTCAAGTGTCTCTCACCGGATTTCTTATGTTAGAAATTGTGTTGGGACTTGGCAGCAAC
CTCACTGTATTGGTACTTTACTGCATGAAATCCAACTTAATCAACTCTGTCAGTAACAT
TATTACAATGAATCTTCATGTACTTGATGTAATAATTTGTGTGGGATGTATTCCTCTAA
CTATAGTTATCCTTCTGCTTTCACTGGAGAGTAACACTGCTCTCATTTGCTGTTTCCAT
GAGGCTTGTGTATCTTTTGCAAGTGTCTCAACAGCAATCAACGTTTTTGCTATCACTTT
GGACAGATATGACATCTCTGTAAAACCTGCAAACCGAATTCTGACAATGGGCAGAGCTG
TAATGTTAATGATATCCATTTGGATTTTTTCTTTTTTCTCTTTCCTGATTCCTTTTATT
GAGGTAAATTTTTTCAGTCTTCAAAGTGGAAATACCTGGGAAAACAAGACACTTTTATG
TGTCAGTACAAATGAATACTACACTGAACTGGGAATGTATTATCACCTGTTAGTACAGA
TCCCAATATTCTTTTTCACTGTTGTAGTAATGTTAATCACATACACCAAAATACTTCAG
GCTCTTAATATTCGAATAGGCACAAGATTTTCAACAGGGCAGAAGAAGAAAGCAAGAAA
GAAAAAGACAATTTCTCTAACCACACAACATGAGGCTACAGACATGTCACAAAGCAGTG
GTGGGAGAAATGTAGTCTTTGGTGTAAGAACTTCAGTTTCTGTAATAATTGCCCTCCGG
CGAGCTGTGAAACGACACCGTGAACGACGAGAAAGACAAAAGAGAGTCTTCAGGATGTC
TTTATTGATTATTTCTACATTTCTTCTCTGCTGGACACCAATTTCTGTTTTAAATACCA
CCATTTTATGTTTAGGCCCAAGTGACCTTTTAGTAAAATTAAGATTGTGTTTTTTAGTC
ATGGCTTATGGAACAACTATATTTCACCCTCTATTATATGCATTCACTAGACAAAAATT
TCAAAAGGTCTTGAAAAGTAAAATGAAAAAGCGAGTTGTTTGTGCGGCCGCACGGGGAC
GCACCCCACCCAGCCTGGGTCCCCAAGATGAGTCCTGCACCACCGCCAGCTCCTCCCTG
GCCAAGGACACTTCATCGTGA
(SEQ ID No: 59)

FIGS. 6A - 6C

~~FIGURE 6~~

A. Amino acid sequence of the β_2AR-V2R chimera

MGQPGNGSAFLLAPNRSHAPDHDVTQQRDEVWVVGMGIVMSLIVLAIVFGNVLVITAI
AKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMKMWTFGNFWCEFWTSIDVLC
VTASIETLCVIAVDRYFAITSPFKYQSLLTKNKARVIILMVWIVSGLTSFLPIQMHWYRAT
HQEAINCYANETCCDFFTNQAYAIASSIVSFYVPLVIMVFVYSRVFQEAKRQLQKIDKSE
GRFHVQNLSQVEQDGRTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIVNIVHV
IQDNLIRKEVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELLCARGRTPPSLGPQDESCTT
ASSSLAKDTSS
(Seq. ID No. 60)

B. Amino acid sequence of the MOR-V2R chimera

MDSSTGPGNTSDCSDPLAQASCSPAPGSWLNLSHVDGNQSDPCGLNRTGLGGNDSLCP
QTGSPSMVTAITIMALYSIVCVVGLFGNFLVMYVIVRYTKMKTATNIYIFNLALADALAT
STLPFQSVNYLMGTWPFGTILCKIVISIDYYNMFTSIFTLCTMSVDRYIAVCHPVKALDFR
TPRNAKIVNVCNWILSSAIGLPVMFMATTKYRQGSIDCTLTFSHPTWYWENLLKICVFIF
AFIMPILIITVCYGLMILRLKSVRMLSGSKEKDRNLRRITRMVLVVVAVFIVCWTPIHIYVI
IKALITIPETTFQTVSWHFCIALGYTNSCLNPVLYAFLDENFKRCFREFCAAARGRTPPSL
GPQDESCTTASSSLAKDTSS
(Seq. ID No. 61)

C. Amino acid sequence of the D1AR-V2R chimera

MAPNTSTMDEAGLPAERDFSFRILTACFLSLLILSTLLGNTLVCAAVIRFRHLRSKVTNFF
VISLAVSDLLVAVLVMPWKAVAEIAGFWPFGSFCNIWVAFDIMCSTASILNLCVISVDRY
WAISSPFQYERKMTPKAAFILISVAWTLSVLISFIPVQLSWHKAKPTWPLDGNFTSLEDTE
DDNCDTRLSRTYAISSSLISFYIPVAIMIVTYTSIYRIAQKQIRRISALERAAVHAKNCQTT
AGNGNPVECAQSESSFKMSFKRETKVLKTLSVIMGVFVCCWLPFFISNCMVPFCGSEET
QPFCIDSITFDVFVWFGWANSSLNPIIYAFNADFQKAFSTLLGCYRLCAAARGRTPPSLGP
QDESCTTASSSLAKDTSS
(Seq. ID No. 62)

FIGS. 6D-6F

~~Figure 6 (cont.)~~

D. Amino acid sequence of the 5HT1AR-V2R chimera

MDVLSPGQGNNTTSPPAPFETGGNTTGISDVTVSYQVITSLLLGTLIFCAVLGNACVVAA
IALERSLQNVANYLIGSLAVTDLMVSVLVLPMAALYQVLNKWTLGQVTCDLFIALDVL
CCTSSILHLCAIALDRYWAITDPIDYVNKRTPRRAAALISLTWLIGFLISIPPMLGWRTPED
RSDPDACTISKDHGYTIYSTFGAFYIPLLLMLVLYGRIFRAARFRIRKTVKKVEKTGADT
RHGASPAPQPKKSVNGESGSRNWRLGVESKAGGALCANGAVRQGDDGAALEVIEVHR
VGNSKEHLPLPSEAGPTPCAPASFERKNERNAEAKRKMALARERKTVKTLGIIMGTFILC
WLPFFIVALVLPFCESSCHMPTLLGAIINWLGYSNSLLNPVIYAYFNKDFQNAFKKIIKCN
FCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(Seq. ID No. 63)

E. Amino acid sequence of the β3AR-V2R chimera

MAPWPHENSSLAPWPDLPTLAPNTANTSGLPGVPWEAALAGALLALAVLATVGGNLLV
IVAIAWTPRLQTMTNVFVTSLAAADLVMGLLVVPPAATLALTGHWPLGATGCELWTSV
DVLCVTASIETLCALAVDRYLAVTNPLRYGALVTKRCARTAVVLVWVVSAAVSFAPIM
SQWWRVGADAEAQRCHSNPRCCAFASNMPYVLLSSSVSFYLPLLVMLFVYARVFVVA
TRQLRLLRGELGRFPPEESPPAPSRSLAPAPVGTCAPPEGVPACGRRPARLLPLREHRALC
TLGLIMGTFTLCWLPFFLANVLRALGGPSLVPGPAFLALNWLGYANSAFNPLIYCRSPDF
RSAFRRLLCRCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(Seq. ID No. 64)

F. Amino acid sequence of the Edg1R-V2R chimera

MGPTSVPLVKAHRSSVSDYVNYDIIVRHYNYTGKLNISADKENSIKLTSVVFILICCFIILE
NIFVLLTIWKTKKFHRPMYYFIGNLALSDLLAGVAYTANLLLSGATTYKLTPAQWFLRE
GSMFVALSASVFSLLAIAIERYITMLKMKLHNGSNNFRLFLLISACWVISLILGGLPIMGW
NCISALSSCSTVLPLYHKHYILFCTTVFTLLLLSIVILYCRIYSLVRTRSRRLTFRKNISKAS
RSSEKSLALLKTVIIVLSVFIACWAPLFILLLLDVGCKVKTCDILFRAEYFLVLAVLNSGT
NPIIYTLTNKEMRRAFIRIMSCCKCAAARGRTPPSLGPQDESCTTASSSLAKDTSS
(Seq. ID No. 65)